FILE 'HOME' ENTERED AT 13:48:17 ON 29 OCT 2001

=> file medline, embase, biosis
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.15	0.15

FILE 'MEDLINE' ENTERED AT 13:48:34 ON 29 OCT 2001

FILE 'EMBASE' ENTERED AT 13:48:34 ON 29 OCT 2001

FILE 'BIOSIS' ENTERED AT 13:48:34 ON 29 OCT 2001

=> s ceramide and sphingomyelin and fgf
L1 0 CERAMIDE AND SPHINGOMYELIN AND FGF

=> s ceramide and fgf
L2 10 CERAMIDE AND FGF

=> duplicate remove l2
DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L2
L3 4 DUPLICATE REMOVE L2 (6 DUPLICATES REMOVED)

=> d 1-4

L3 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
AN 2000259881 MEDLINE
DN 20259881 PubMed ID: 10797307
TI Tumor necrosis factor-alpha-induced apoptosis is associated with suppression of insulin-like growth factor binding protein-5 secretion in differentiating murine skeletal myoblasts.
AU Meadows K A; Holly J M; Stewart C E
CS University Department of Surgery, Bristol Royal Infirmary, Bristol, England.
SO JOURNAL OF CELLULAR PHYSIOLOGY, (2000 Jun) 183 (3) 330-7.
Journal code: HNB; 0050222. ISSN: 0021-9541.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000606
Last Updated on STN: 20000606
Entered Medline: 20000522

L3 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
AN 1999135881 MEDLINE
DN 99135881 PubMed ID: 9950679
TI Interaction of fibroblast growth factor-2 (**FGF**-2) with free gangliosides: biochemical characterization and biological consequences in endothelial cell cultures.
AU Rusnati M; Tanghetti E; Urbinati C; Tulipano G; Marchesini S; Ziche M; Presta M
CS Unit of General Pathology and Immunology, Department of Biomedical Sciences and Biotechnology, School of Medicine, University of Brescia, 25123 Brescia, Italy.
SO MOLECULAR BIOLOGY OF THE CELL, (1999 Feb) 10 (2) 313-27.
Journal code: BAU; 9201390. ISSN: 1059-1524.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 199903
ED Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990318

L3 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:112357 BIOSIS
DN PREV199900112357
TI Insulin-like growth factor binding protein-5 (IGFBP-5) acts as a survival factor during C2 rodent skeletal myoblast differentiation under various stimulatory conditions.
AU Meadows, K.; Holly, J. M. P.; Stewart, C. E. H.
CS Dep. Surgery, B. R. I., Bristol BS2 8HW UK
SO Journal of Endocrinology, (Nov., 1998) Vol. 159, No. SUPPL., pp. P26.
Meeting Info.: 189th Meeting of the Society for Endocrinology London, England, UK November 23-24, 1998
ISSN: 0022-0795.
DT Conference
LA English

L3 ANSWER 4 OF 4 MEDLINE DUPLICATE 3
AN 1998038868 MEDLINE
DN 98038868 PubMed ID: 9373031
TI **FGF**-2 converts mature oligodendrocytes to a novel phenotype.
AU Bansal R; Pfeiffer S E
CS Department of Pharmacology, University of Connecticut Medical School, Farmington 06030-3205, USA.. bansal@panda.uchc.edu
NC NS 10861 (NINDS)
SO JOURNAL OF NEUROSCIENCE RESEARCH, (1997 Oct 15) 50 (2) 215-28. Ref: 80
Journal code: KAC; 7600111. ISSN: 0360-4012.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980112

=> d 1-4 abs

L3 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
AB Wasting of muscle and fat during cachexia exceeds that explained by reduced food intake alone. This wasting may result from an imbalanced cytokine environment, which could lead to increased protein catabolism. Supporting this, tumor necrosis factor-alpha (TNF-alpha) is raised in several animal models of cachectic muscle wasting. Therefore, we assessed the effects of TNF-alpha and its second messenger, **ceramide**, on the proliferation, differentiation, and survival of murine C2 skeletal myoblasts. Because insulin-like growth factor binding protein-5 (IGFBP-5) and insulin-like growth factor-II (IGF-II) are potent regulators of myoblast proliferation and differentiation, we monitored the ability of exogenous TNF-alpha to manipulate this system. Fibroblast growth factor (**FGF**) **ceramide**, or TNF-alpha suppressed differentiation of C2 cells compared with controls. All treatments suppressed IGF-II production but only TNF-alpha blocked IGFBP-5 secretion. TNF-alpha increased apoptotic cell death, which otherwise remained basal (low serum differentiation medium (LSM), **FGF**) or low (**ceramide**). Suppression of both IGFBP-5 and IGF-II secretion may explain why of all

triggers tested, only TNF-alpha not only blocked differentiation, but also promoted cell death. This suggests a fundamental role of IGFBP-5 for maintaining muscle survival. Supporting this hypothesis, no increase in apoptosis was seen in IGFBP-5 cDNA tranfected C2 cells after TNF-alpha treatment. In summary, the IGF system is essential for maintaining skeletal muscle cell survival and differentiation, and its suppression by TNF-alpha is fundamental regarding muscle wasting, and may be associated in vivo with cancer cachexia.

L3 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
AB Exogenous gangliosides affect the angiogenic activity of fibroblast growth factor-2 (**FGF**-2), but their mechanism of action has not been elucidated. Here, a possible direct interaction of sialo-glycolipids with **FGF**-2 has been investigated. Size exclusion chromatography demonstrates that native, but not heat-denatured, 125I-**FGF**-2 binds to micelles formed by gangliosides GT1b, GD1b, or GM1. Also, gangliosides protect native **FGF**-2 from trypsin digestion at micromolar concentrations, the order of relative potency being GT1b > GD1b > GM1 = GM2 = sulfatide > GM3 = galactosyl-**ceramide**, whereas asialo-GM1, neuraminic acid, and N-acetylneuramin-lactose were ineffective. Scatchard plot analysis of the binding data of fluorochrome-labeled GM1 to immobilized **FGF**-2 indicates that **FGF**-2/GM1 interaction occurs with a Kd equal to 6 microM. This interaction is inhibited by the sialic acid-binding peptide mastoparan and by the synthetic fragments **FGF**-2(112-129) and, to a lesser extent, **FGF**-2(130-155), whereas peptides **FGF**-2(10-33), **FGF**-2(39-59), **FGF**-2(86-96), and the basic peptide HIV-1 Tat(41-60) were ineffective. These data identify the COOH terminus of **FGF**-2 as a putative ganglioside-binding region. Exogenous gangliosides inhibit the binding of 125I-**FGF**-2 to high-affinity tyrosine-kinase **FGF**-receptors (FGFRs) of endothelial GM 7373 cells at micromolar concentrations. The order of relative potency was GT1b > GD1b > GM1 > sulfatide a = sialo-GM1. Accordingly, GT1b,GD1b, GM1, and GM2, but not GM3 and asialo-GM1, prevent the binding of 125I-**FGF** -2 to a soluble, recombinant form of extracellular FGFR-1. Conversely, the soluble receptor and free heparin inhibit the interaction of fluorochrome-labeled GM1 to immobilized **FGF**-2. In agreement with their FGFR antagonist activity, free gangliosides inhibit the mitogenic activity exerted by **FGF**-2 on endothelial cells in the same range of concentrations. Also in this case, GT1b was the most effective among the gangliosides tested while asialo-GM1, neuraminic acid, N-acetylneuramin-lactose, galactosyl-**ceramide**, and sulfatide were ineffective. In conclusion, the data demonstrate the capacity of exogenous gangliosides to interact with **FGF**-2. This interaction involves the COOH terminus of the **FGF**-2 molecule and depends on the structure of the oligosaccharide chain and on the presence of sialic acid residue(s) in the ganglioside molecule. Exogenous gangliosides act as **FGF**-2 antagonists when added to endothelial cell cultures. Since gangliosides are extensively shed by tumor cells and reach elevated levels in the serum of tumor-bearing patients, our data suggest that exogenous gangliosides may affect endothelial cell function by a direct interaction with **FGF**-2, thus modulating tumor neovascularization.

L3 ANSWER 3 OF 4 BIOSIS

L3 ANSWER 4 OF 4 MEDLINE DUPLICATE 3
AB Fibroblast growth factor (**FGF**)-2 differentially regulates oligodendrocyte progenitor proliferation and differentiation in culture, and modulates gene expression of its own receptors, in a developmental and receptor type-specific manner (Bansal et al., 1996a,b). Three **FGF** receptors (types 1, 2, 3) are expressed in postmitotic, terminally differentiating oligodendrocytes. Exposure of such cells to **FGF** -2 results in: (a) the down-regulation of myelin-specific gene expression

(e.g., **ceramide** galactosyltransferase, 2',3'-cyclic nucleotide 3'-phosphohydrolase, myelin basic protein, proteolipid protein), (b) dramatic increases in the length of cellular processes in a time- and dose-dependent manner, (c) re-entrance into the cell cycle without accompanying mitosis, and (d) the alteration of the expression of both low- and high-affinity **FGF** receptors. Compared to oligodendrocyte progenitors, the differentiated oligodendrocytes treated with **FGF**-2 incorporate BrdU at a slower rates, exhibit different patterns of both **FGF** high- and low-affinity (syndecans) receptors, and are morphologically very different. In addition, they do not re-express the progenitor markers A2B5, NG2 or PDGFalpha receptor. Therefore, although the **FGF**-treated cells lose their differentiated OL/myelin markers, they do not revert to progenitors and clearly represent a different, apparently novel, phenotype both morphologically and biochemically, which we have termed NOLs. These data indicate that terminally differentiated oligodendrocytes retain the plasticity to reprogram their differentiation fate under the influence of environmental factors. The possible significance of this response to **FGF** relative to normal and pathological physiology is discussed. In particular, on the basis of these data we predict the appearance of cells in and around multiple sclerosis plaques with the phenotype O4+, NG2-, A2B5-, O1-, MBP-.

```
=> s fgf and apoptosis
L4          466 FGF AND APOPTOSIS

=> s l4 and sepsis
L5            3 L4 AND SEPSIS

=> duplicate remove l5
DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L5
L6             1 DUPLICATE REMOVE L5 (2 DUPLICATES REMOVED)

=> d

L6   ANSWER 1 OF 1     MEDLINE                              DUPLICATE 1
AN   2001104470     MEDLINE
DN   20547414   PubMed ID: 11095643
TI   Basic fibroblast growth factor selectively enhances TNF-alpha-induced
     apoptotic cell death in glomerular endothelial cells: effects on apoptotic
     signaling pathways.
AU   Messmer U K; Briner V A; Pfeilschifter J
CS   Pharmacenter Frankfurt, Klinikum der Johann Wolfgang Goethe-University
     Hospital, Frankfurt am Main, Germany.
SO   JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (2000 Dec) 11 (12)
     2199-211.
     Journal code: A6H. ISSN: 1046-6673.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200102
ED   Entered STN: 20010322
     Last Updated on STN: 20010322
     Entered Medline: 20010208

=> d abs

L6   ANSWER 1 OF 1     MEDLINE                              DUPLICATE 1
AB   Endothelial cell damage of glomeruli and kidney arterioles seems to play a
```

pivotal role in several pathologic situations, such as Gram-negative **sepsis**, glomerulonephritis, and acute renal failure. Bacterial lipopolysaccharide (LPS) and tumor necrosis factor-alpha (TNF-alpha) have been identified as potent inducers of apoptotic cell death in bovine glomerular endothelial cells. Both agents elicited apoptotic DNA laddering within 12 to 24 h. Basic fibroblast growth factor (bFGF) was generally described as a protective factor for endothelial cells against radiation-, TNF-alpha-, and UV-light-induced programmed cell death. Therefore, whether bFGF also affects **apoptosis** of microvascular endothelial cells was questioned. Surprising was that simultaneous treatment of glomerular endothelial cells with bFGF and either LPS or TNF-alpha left LPS-induced death unaffected, whereas TNF-alpha-induced death induction was potentiated, amounting to 48.9+/-6.3% versus 22.4+/-4.3% DNA degradation with TNF-alpha alone. Comparably, acidic **FGF** also selectively potentiated TNF-alpha-induced **apoptosis**. In mechanistic terms, bFGF synergistically increased TNF-alpha-induced mitochondrial permeability transition, the release of cytochrome c from mitochondria to the cytosol, and upregulation of the proapoptotic protein Bak and significantly enhanced activation of caspase-8 protease activity. In contrast, stress-activated protein kinase and nuclear factor kappaB activation, which represent primary signals of TNF/TNF receptor interaction, downregulation of the antiapoptotic protein Bcl-x(L), and caspase-3-like protease activation, were unaffected. As bFGF did not affect LPS-induced apoptotic cell death, bFGF also left LPS-induced Bak upregulation and Bcl-x(L) downregulation unaffected. The results point to a selective bFGF-mediated enhancement of distinct proapoptotic pathways induced by TNF-alpha in glomerular endothelial cells.

```
=> s bfgf or fgf-2
L7       17494 BFGF OR FGF-2

=> s l7 and sepsis
L8           6 L7 AND SEPSIS

=> duplicate remove l8
DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L8
L9            2 DUPLICATE REMOVE L8 (4 DUPLICATES REMOVED)

=> d 1-2

L9   ANSWER 1 OF 2     MEDLINE                              DUPLICATE 1
AN   2001104470     MEDLINE
DN   20547414   PubMed ID: 11095643
TI   Basic fibroblast growth factor selectively enhances TNF-alpha-induced
     apoptotic cell death in glomerular endothelial cells: effects on apoptotic
     signaling pathways.
AU   Messmer U K; Briner V A; Pfeilschifter J
CS   Pharmacenter Frankfurt, Klinikum der Johann Wolfgang Goethe-University
     Hospital, Frankfurt am Main, Germany.
SO   JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (2000 Dec) 11 (12)
     2199-211.
     Journal code: A6H. ISSN: 1046-6673.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200102
ED   Entered STN: 20010322
     Last Updated on STN: 20010322
     Entered Medline: 20010208
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L9 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
AN 1999262477 MEDLINE
DN 99262477 PubMed ID: 10328964
TI Tumor necrosis factor-alpha and basic fibroblast growth factor differentially inhibit the insulin-like growth factor-I induced expression of myogenin in C2C12 myoblasts.
AU Layne M D; Farmer S R
CS Department of Biochemistry, Boston University School of Medicine, Boston, Massachusetts 02118, USA.
NC DK45058 (NIDDK)
HL07035 (NHLBI)
SO EXPERIMENTAL CELL RESEARCH, (1999 May 25) 249 (1) 177-87.
Journal code: EPB; 0373226. ISSN: 0014-4827.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199906
ED Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990609

=> d 2 abs

L9 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
AB Tumor necrosis factor-alpha (TNF-alpha) plays a role in several disease states such as **sepsis**, cachexia, and non-insulin-dependent diabetes. TNF-alpha interferes with insulin signaling and inhibits differentiation-specific gene expression in adipose tissue and skeletal muscle. We have examined the mechanisms by which TNF-alpha, in comparison to basic fibroblast growth factor (**bFGF**), inhibits the insulin-like growth factor-I (IGF-I)-induced differentiation of C2C12 myoblasts. Adhesion of quiescent, suspended myoblasts to collagen in high concentrations of IGF-I (10 nM) induced these cells to proliferate during the initial 24 h postplating and in so doing transiently inhibited the expression of myogenin, an essential transcription factor controlling myoblast differentiation. Low doses of IGF-I (1 nM) were minimally mitogenic and enhanced muscle-specific gene expression. Quiescent myoblasts treated with **bFGF** in combination with IGF-I did not express myogenin, but expressed proliferating cell nuclear antigen and underwent DNA synthesis. In contrast, TNF-alpha in the presence or absence of 1 nM IGF-I, did not stimulate DNA synthesis in myoblasts. However, TNF-alpha inhibited myogenin mRNA and protein expression. Expression of the cyclin-dependent kinase inhibitor p21 correlated with myogenin expression and myoblast differentiation, but not with growth arrest. These results indicate that both TNF-alpha and **bFGF** inhibit myogenin expression but differentially influence myoblast proliferation.

=> s sphingomyelin and (bfgf or fgf-2
UNMATCHED LEFT PARENTHESIS 'AND (BFGF'
The number of right parentheses in a query must be equal to the number of left parentheses.

=> s sphingomyelin and (bfgf or fgf-2)
L10 10 SPHINGOMYELIN AND (BFGF OR FGF-2)

=> duplicate remove l10
DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L10
L11 4 DUPLICATE REMOVE L10 (6 DUPLICATES REMOVED)

=> d 1-4

L11 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
AN 2001308598 MEDLINE
DN 21201111 PubMed ID: 11278937
TI Basic fibroblast growth factor-induced proliferation of primary astrocytes. evidence for the involvement of **sphingomyelin** biosynthesis.
AU Riboni L; Viani P; Bassi R; Giussani P; Tettamanti G
CS Department of Medical Chemistry and Biochemistry, Study Center for the Functional Biochemistry of Brain Lipids, University of Milan, via Fratelli Cervi 93, LITA-Segrate, Segrate, 20090 Milan, Italy.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Apr 20) 276 (16) 12797-804.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

L11 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
AN 2001400864 MEDLINE
DN 21345407 PubMed ID: 11452123
TI Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice.
CM Comment in: Science. 2001 Jul 13;293(5528):227-8
AU Paris F; Fuks Z; Kang A; Capodieci P; Juan G; Ehleiter D; Haimovitz-Friedman A; Cordon-Cardo C; Kolesnick R
CS Laboratory of Signal Transduction and, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.
NC CA52462 (NCI)
CA85704 (NCI)
SO SCIENCE, (2001 Jul 13) 293 (5528) 293-7.
Journal code: UJ7; 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200107
ED Entered STN: 20010730
Last Updated on STN: 20010730
Entered Medline: 20010726

L11 ANSWER 3 OF 4 MEDLINE DUPLICATE 3
AN 2000209350 MEDLINE
DN 20209350 PubMed ID: 10744663
TI Up-regulation of glucosylceramide synthesis upon stimulation of axonal growth by basic fibroblast growth factor. Evidence for post-translational modification of glucosylceramide synthase.
AU Boldin S A; Futerman A H
CS Department of Biological Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Apr 7) 275 (14) 9905-9.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005

ED Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000508

L11 ANSWER 4 OF 4 MEDLINE DUPLICATE 4
AN 1998370368 MEDLINE
DN 98370368 PubMed ID: 9706871
TI Sphingosine modulates interleukin-6 synthesis in osteoblasts.
AU Kozawa O; Tokuda H; Matsuno H; Uematsu T
CS Department of Pharmacology, Gifu University School of Medicine, Japan.
SO JOURNAL OF CELLULAR BIOCHEMISTRY, (1998 Sep 1) 70 (3) 338-45.
Journal code: HNF; 8205768. ISSN: 0730-2312.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199810
ED Entered STN: 19981029
Last Updated on STN: 19981029
Entered Medline: 19981020

=> d 1-4 abs

L11 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
AB We recently reported that the marked decrease in cellular ceramide in primary astrocytes is an early event associated with the mitogenic activity of basic fibroblast growth factor (**bFGF**) (Riboni, L., Viani, P., Bassi, R., Stabieini, A., and Tettamanti, G. (2000) GLIA 32, 137-145). Here we show that a rapid activation of **sphingomyelin** biosynthesis appears to be the major mechanism responsible for the fall in ceramide levels induced by **bFGF**. When quiescent astrocytes were treated with **bFGF**, an increased amount of newly synthesized ceramide (from either l-[(3)H]serine or [(3)H]sphingosine) was directed toward the biosynthesis of **sphingomyelin**. Conversely, **bFGF** did not appear to affect ceramide levels by other metabolic pathways involved in ceramide turnover such as **sphingomyelin** degradation and ceramide biosynthesis, degradation, and glucosylation. Enzymatic studies demonstrating a relevant and rapid increase in **sphingomyelin** synthase activity after **bFGF** treatment have provided a convincing explanation for the activation of **sphingomyelin** biosynthesis. The **bFGF**-induced increase in **sphingomyelin** synthase appears to depend on a post-translational activation mechanism. Moreover, in the presence of brefeldin A, the activation of **sphingomyelin** biosynthesis was abolished, suggesting that the enzyme is located in a compartment other than the Golgi apparatus. Also the phosphatidylcholine-specific phospholipase C inhibitor D609 exerted a potent inhibitory effect on **sphingomyelin** biosynthesis. Finally, we demonstrate that inhibition of **sphingomyelin** biosynthesis by brefeldin A or D609 led to a significant inhibition of **bFGF**-stimulated mitogenesis. All this supports that, in primary astrocytes, the early activation of **sphingomyelin** synthase is involved in the **bFGF** signaling pathway leading to proliferation.

L11 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
AB Gastrointestinal (GI) tract damage by chemotherapy or radiation limits their efficacy in cancer treatment. Radiation has been postulated to target epithelial stem cells within the crypts of Lieberkuhn to initiate the lethal GI syndrome. Here, we show in mouse models that microvascular endothelial apoptosis is the primary lesion leading to stem cell dysfunction. Radiation-induced crypt damage, organ failure, and death from the GI syndrome were prevented when endothelial apoptosis was inhibited pharmacologically by intravenous basic fibroblast growth factor (

bFGF) or genetically by deletion of the acid sphingomyelinase gene. Endothelial, but not crypt, cells express FGF receptor transcripts, suggesting that the endothelial lesion occurs before crypt stem cell damage in the evolution of the GI syndrome. This study provides a basis for new approaches to prevent radiation damage to the bowel.

L11 ANSWER 3 OF 4 MEDLINE DUPLICATE 3
AB We have previously shown that ongoing glucosylceramide (GlcCer) synthesis is required for basic fibroblast growth factor (**bFGF**) and laminin to stimulate axonal growth in cultured hippocampal neurons (Boldin, S., and Futerman, A. H. (1997) J. Neurochem. 68, 882-885). We now demonstrate that stimulation of axonal growth by **bFGF** leads to an increase in the rate of GlcCer synthesis. Within minutes of incubation with **bFGF**, a significant increase in the rate of metabolism of [(14)C]hexanoyl ceramide to [(14)C]hexanoyl GlcCer is detected, but there are no changes in the rate of [(14)C]hexanoyl **sphingomyelin** synthesis. In vitro analysis of GlcCer synthase activity revealed an approximately 2-fold increase in the rate of [(14)C]hexanoyl GlcCer synthesis upon incubation with either **bFGF** or laminin; other growth factors, which did not effect the rate of axon growth, had no effect on the rate of [(14)C]hexanoyl GlcCer synthesis. The increased rate of [(14)C]hexanoyl GlcCer synthesis was not affected by preincubation with either cycloheximide or actinomycin, and no elevation of GlcCer synthase mRNA levels was detected, suggesting that GlcCer synthase is up-regulated by a post-translational mechanism. The relevance of these results for understanding the regulation of axonal growth is discussed.

L11 ANSWER 4 OF 4 MEDLINE DUPLICATE 4
AB We previously reported that prostaglandin (PG)E1 and PGF2alpha induce the synthesis of interleukin-6 (IL-6) via activation of protein kinase (PK)A and PKC, respectively, in osteoblast-like MC3T3-E1 cells. In addition, we have shown that basic fibroblast growth factor (**bFGF**) elicits IL-6 synthesis through intracellular Ca2+ mobilization in these cells and that tumor necrosis factor-alpha (TNF) induces IL-6 synthesis through sphingosine 1-phosphate produced by **sphingomyelin** hydrolysis. In the present study, among **sphingomyelin** metabolites, we examined the effect of sphingosine on IL-6 synthesis induced by various agonists in MC3T3-E1 cells. Sphingosine inhibited the IL-6 synthesis induced by PGF2alpha or 12-O-tetradecanoylphorbol-13-acetate, an activator of PKC. Sphingosine suppressed the PGE1-induced IL-6 synthesis. The IL-6 synthesis induced by cholera toxin, forskolin, or dibutyryl cAMP was inhibited by sphingosine. Sphingosine inhibited the IL-6 synthesis induced by **bFGF** or A23187. However, sphingosine did not affect the IL-6 synthesis induced by interleukin-1. On the contrary, sphingosine enhanced the TNF-induced IL-6 synthesis. DL-threo-Dihydrosphingosine, an inhibitor of sphingosine kinase, reduced the enhancement by sphingosine as well as the TNF-effect. These results indicate that sphingosine modulates the IL-6 synthesis stimulated by various agonists in osteoblasts.

```
=> s sphingomyelin and sepsis
L12          28 SPHINGOMYELIN AND SEPSIS

=> duplicate remove l12
DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L12
L13           19 DUPLICATE REMOVE L12 (9 DUPLICATES REMOVED)

=> d 1-19

L13  ANSWER 1 OF 19  BIOSIS  COPYRIGHT 2001 BIOSIS
AN   2001:167509  BIOSIS
DN   PREV200100167509
```

TI Spontaneous versus corticosteroid-induced lung maturity: Is there a difference in neonatal outcome.
AU Locatelli, Anna (1); Patane, Luisa; Vergani, Patrizia; Ratti, Marta; Colombo, Carla (1); Ghidini, Alessandro
CS (1) Neonatology, University of Milano-Bicocca, Monza Italy
SO American Journal of Obstetrics and Gynecology, (January, 2001) Vol. 184, No. 1, pp. S48. print.
Meeting Info.: 21st Annual Meeting of the Society for Maternal-Fetal Medicine Reno, Nevada, USA February 05-10, 2001
ISSN: 0002-9378.
DT Conference
LA English
SL English

L13 ANSWER 2 OF 19 MEDLINE
AN 2001416470 MEDLINE
DN 21357595 PubMed ID: 11465070
TI Modulation of the ceramide level, a novel therapeutic concept?.
AU Claus R; Russwurm S; Meisner M; Kinscherf R; Deigner H P
CS Institute of Pharmaceutical Chemistry, University of Heidelberg, Germany.
SO Curr Drug Targets, (2000 Sep) 1 (2) 185-205. Ref: 225
Journal code: D3U; 100960531. ISSN: 1389-4501.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010903
Last Updated on STN: 20010903
Entered Medline: 20010830

L13 ANSWER 3 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999418681 EMBASE
TI Tumor necrosis factor-.alpha., sphingosine, ceramide: Which is the appropriate marker of inflammation?.
AU Horton J.W.
CS Dr. J.W. Horton, Univ. of Texas Southwest Med. Center, Dallas, TX, United States
SO Critical Care Medicine, (1999) 27/11 (2580-2581).
Refs: 22
ISSN: 0090-3493 CODEN: CCMDC7
CY United States
DT Journal; Editorial
FS 004 Microbiology
005 General Pathology and Pathological Anatomy
024 Anesthesiology
029 Clinical Biochemistry
LA English

L13 ANSWER 4 OF 19 MEDLINE DUPLICATE 1
AN 2000043858 MEDLINE
DN 20043858 PubMed ID: 10579257
TI Ceramide concentrations in septic patients: a possible marker of multiple organ dysfunction syndrome.
CM Comment in: Crit Care Med. 1999 Nov;27(11):2580-1
AU Delogu G; Famularo G; Amati F; Signore L; Antonucci A; Trinchieri V; Di Marzio L; Cifone M G
CS Institute of Anesthesia and Intensive Care, La Sapienza University, Rome, Italy.
SO CRITICAL CARE MEDICINE, (1999 Nov) 27 (11) 2413-7.
Journal code: DTF; 0355501. ISSN: 0090-3493.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
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L13 ANSWER 5 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999282015 EMBASE
TI Cytokines and septic myocardial depression: Nitric oxide versus sphingosine/ceramide?.
AU Kumar A.; Kumar A.; Parrillo J.E.
CS Dr. A. Kumar, R.-Presbyterian-St. Luke's Med. Ctr., Chicago, IL, United States
SO Critical Care Medicine, (1999) 27/7 (1391-1393).
Refs: 18
ISSN: 0090-3493 CODEN: CCMDC7
CY United States
DT Journal; Editorial
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
LA English

L13 ANSWER 6 OF 19 MEDLINE DUPLICATE 2
AN 1999374491 MEDLINE
DN 99374491 PubMed ID: 10446825
TI Tumor necrosis factor-alpha and interleukin-1beta synergistically depress human myocardial function.
CM Comment in: Crit Care Med. 1999 Jul;27(7):1391-3
AU Cain B S; Meldrum D R; Dinarello C A; Meng X; Joo K S; Banerjee A; Harken A H
CS Department of Surgery, University of Colorado Health Sciences Center, Denver 80262, USA.
NC GM-08315 (NIGMS)
HL-43696 (NHLBI)
HL-44186 (NHLBI)
SO CRITICAL CARE MEDICINE, (1999 Jul) 27 (7) 1309-18.
Journal code: DTF; 0355501. ISSN: 0090-3493.
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(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199908
ED Entered STN: 19990913
Last Updated on STN: 19990913
Entered Medline: 19990830

L13 ANSWER 7 OF 19 MEDLINE
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DN 99314729 PubMed ID: 10454830
TI Macrophage TNF mRNA expression induced by LPS is regulated by **sphingomyelin** metabolites.
AU Lo C J; Fu M; Lo F R; Cryer H G
CS Department of Surgery, University of California, Los Angeles 90095-6904, USA.. clo@surgery.medsch.ucla.edu
SO SHOCK, (1999 Jun) 11 (6) 411-5.
Journal code: CAE; 9421564. ISSN: 1073-2322.
CY United States
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EM 199908
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L13 ANSWER 8 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
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CY United States
DT Journal; Article
FS 002 Physiology
LA English
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L13 ANSWER 9 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
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AU Macones G.A.; Bader T.J.; Asch D.A.
CS Dr. G.A. Macones, Clinical Epidemiol./Biostatist. Ctr., 901 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19,104-6021, United States
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CY United Kingdom
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FS 010 Obstetrics and Gynecology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English

L13 ANSWER 10 OF 19 MEDLINE DUPLICATE 4
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DN 98161769 PubMed ID: 9502662
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CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
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LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980507
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L13 ANSWER 11 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
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CS E.D. Ceppi, School of Biological Sciences, University of Sussex, Brighton BN1 9QG, United Kingdom
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LA English

L13 ANSWER 12 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
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Refs: 10
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CY United States
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FS 007 Pediatrics and Pediatric Surgery
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TI Protection from endotoxic shock in mice by pharmacologic inhibition of phosphatidic acid.
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026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English

L13 ANSWER 14 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
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FS 005 General Pathology and Pathological Anatomy
009 Surgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry

030 Pharmacology
037 Drug Literature Index
LA English
SL English

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CY Australia
DT Journal; Article; (JOURNAL ARTICLE)
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ED Entered STN: 19920424
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CS Department of Obstetrics and Gynecology, University of South Florida, Orlando Regional Medical Center.
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CY United States
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EM 198905
ED Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890524

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CS Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM 87131, United States
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CODEN: AJHEDD
CY United States
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LA English

L13 ANSWER 19 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
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CS Dept. Anesth. Reanimat. Bobigny-Bondy, Hop. Avicenne, 93009 Bobigny, France
SO Annales de l'Anesthesiologie Francaise, (1980) 21/4 (451-458).
CODEN: AANFAE
CY France
DT Journal
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029 Clinical Biochemistry
004 Microbiology
LA French
SL English

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L13 ANSWER 1 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AB OBJECTIVE: To assess whether cases of fetal lung maturity naturally occurring have distinguishing characteristics compared with cases of lung maturity following antenatal corticosteroid therapy. STUDY DESIGN: From a database of all singleton pregnancies delivered at <37 weeks between January 1993 and December 1999, we selected those with a documented L/S ratio gtoreq 2 (n = 178), and we then stratified them according to whether or not maternal corticosteroid had been administered before amniocentesis for lung maturity assessment. Obstetric and neonatal characteristics were compared between the 2 groups. Statistical methods included chi2 test, Fisher's exact test, Student t test, and regression analysis, with P < .05 considered significant. RESULTS: Of the 178 pregnancies meeting entry criteria, 99 (55%) received antenatal corticosteroid therapy and 79 (45%) did not. Mean standard deviation gestational age at delivery (32.1 +- 2.2 weeks vs 33.0 +- 2.2 weeks, P = .01), birth weight (1664 +- 524 g vs 1835 +- 679 g, P = .06), and cord arterial pH (7.29 +- 0.08 vs 7.32 +- 0.07, P = .01) were lower in the corticosteroid-induced than spontaneous lung maturity group. The 2 groups were similar for indication for preterm delivery, mode of delivery, rates of 5-minute Apgar score <7, neonatal intraventricular hemorrhage, respiratory distress syndrome, and **sepsis**. CONCLUSIONS: Fetal lung maturation achieved with corticosteroids results in a neonatal outcome similar to that following spontaneous lung maturation, despite a lower gestational age. However, the observed difference in cord blood gases between the 2 groups deserves further studies.

L13 ANSWER 2 OF 19 MEDLINE
AB The **sphingomyelin** (SM) pathway is an ubiquitous and evolutionarily conserved signaling system in which ceramide (CA), generated from SM by the action of various isoforms of sphingomyelinases (SMases) functions as an important second messenger. Recent evidence suggests that branching pathways of sphingolipid metabolism mediate either apoptotic or mitogenic responses depending on cell type and the nature of the stimulus. Events involving SM metabolites and CA in particular include proliferation, differentiation and growth arrest as well as the induction of apoptosis. An improved understanding of SMase-dependent signaling may afford relevant insights into the pathogenesis of diseases and provide novel strategies and selective targets for a therapeutic intervention e.g. in cancer, cardiovascular and neurodegenerative diseases, HIV and septic shock. This article briefly summarizes the role of SMases in signaling pathways, its potential contribution in the development and maintenance of various pathobiological states and analyzes the perspective of a potentially isotype-specifc inhibition of SMases as a novel therapeutic concept.

L13 ANSWER 3 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

L13 ANSWER 4 OF 19 MEDLINE DUPLICATE 1
AB OBJECTIVES: To investigate the concentrations of mononuclear cell-associated ceramide and serum tumor necrosis factor-alpha (TNF-alpha) in patients with **sepsis** and to assess their predictive value for the development of multiple organ dysfunction syndrome (MODS). DESIGN: Prospective, cohort study. SETTING: Intensive care unit and two research laboratories at a university hospital. PATIENTS: Twenty-three adult patients admitted to an intensive care unit meeting the criteria for diagnosis of **sepsis**. INTERVENTIONS: Blood samples were collected at the time when diagnosis of **sepsis** was made. MEASUREMENTS AND MAIN RESULTS: Mononuclear cell-associated ceramide and serum TNF-alpha were significantly elevated in the samples from the septic patients compared with the control individuals (318.01+/-270.15 pmol/10(6) cells vs. 99.90+/-52.75 pmol/10(6) cells; p<.001, and 28.52+/-18.77 pg/mL vs. 10.43+/-3.37 pg/mL; p<.0001, respectively), and a direct correlation linked ceramide and TNF-alpha concentrations (r2 = .90, p<.00001). In the septic patients who went on to develop MODS, ceramide and TNF-alpha were significantly higher compared with the no MODS patients (489.22+/-264.93 pmol/10(6) cells vs. 131.23+/-99.02 pmol/10(6) cells; p<.0001, and 40.96+/-18 pg/mL vs. 14.95+/-5.60 pg/mL; p<.001, respectively). The receiver operating characteristic curves demonstrated that both TNF-alpha and ceramide were prognostic of MODS, but ceramide concentrations were more efficient predictors. CONCLUSIONS: These observations suggest that mononuclear cells of peripheral blood from patients with **sepsis** are committed to undergo apoptosis, because there is evidence that ceramide acts as an endogenous mediator of apoptosis. The strong correlation we found between cell-associated ceramide and serum TNF-alpha supports the hypothesis that this cytokine plays an important role in activating the **sphingomyelin** pathway and ceramide generation in patients with **sepsis**. In addition, this study provides evidence that consistent concentrations of mononuclear cell-associated ceramide may predict progression toward MODS in septic patients. KEY WORDS: ceramide; tumor necrosis factor; outcome; apoptosis; multiple organ dysfunction syndrome; critical illness; mononuclear cells; intensive care unit (ICU); **sphingomyelin** pathway

L13 ANSWER 5 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

L13 ANSWER 6 OF 19 MEDLINE DUPLICATE 2
AB OBJECTIVE: Proinflammatory cytokines such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-1beta have been implicated in the pathogenesis of myocardial dysfunction in ischemia-reperfusion injury,

sepsis, chronic heart failure, viral myocarditis, and cardiac allograft rejection. Although circulating TNF-alpha and IL-1beta are both often elevated in septic shock, it remains unknown whether TNF-alpha or IL-1beta are the factors induced during **sepsis** that directly depress human myocardial function, and if so, whether the combination synergistically depresses myocardial function. Furthermore, the mechanism(s) by which these cytokines induce human myocardial depression remain unknown. We hypothesized the following: a) TNF-alpha and IL-1beta directly depress human myocardial function; b) together, TNF-alpha and IL-1beta act synergistically to depress human myocardial function; and c) inhibition of ceramidase or nitric oxide synthase attenuates myocardial depression induced by TNF-alpha or IL-1beta by limiting proximal cytokine signaling or production of myocardial nitric oxide (NO). DESIGN: Prospective, randomized, controlled study. SETTING: Experimental laboratory in a university hospital. SUBJECTS: Freshly obtained human myocardial trabeculae. INTERVENTIONS: Human atrial trabeculae were obtained at the time of cardiac surgery, suspended in organ baths, and field simulated at 1 Hz, and the developed force was recorded. After a 90-min equilibration, TNF-alpha (1.25, 12.5, 125, or 250 pg/mL for 20 mins), IL-1beta (6.25, 12.5, 50, or 200 pg/mL for 20 mins), or TNF-alpha (1.25 pg/mL) plus IL-1beta (6.25 pg/mL) were added to the bath, and function was measured for the subsequent 100 mins after the 20-min exposure. To assess the roles of the **sphingomyelin** and NO pathways in TNF-alpha and IL-1beta cross-signaling, the ceramidase inhibitor N-oleoyl ethanolamine (1 microM) or the NO synthase inhibitor N(G)-monomethyl-L-arginine (10 microM) was added before TNF-alpha (125 pg/mL) or IL-1beta (50 pg/mL). MEASUREMENTS AND MAIN RESULTS: TNF-alpha and IL-1beta each depressed human myocardial function in a dose-dependent fashion (maximally depressing to 16.2 + 1.9% baseline developed force for TNF-alpha and 25.7 + 6.3% baseline developed force for IL-1beta), affecting systolic relatively more than diastolic performance (each $p < .05$). However, when combined, TNF-alpha and IL-1beta at concentrations that did not individually result in depression ($p > .05$ vs. control) resulted in contractile depression ($p < .05$ vs. control). Inhibition of myocardial sphingosine or NO release abolished the myocardial depressive effects of either TNF-alpha or IL-1beta. CONCLUSIONS: TNF-alpha and IL-1beta separately and synergistically depress human myocardial function. Sphingosine likely participates in the TNF-alpha and IL-1beta signal leading to human myocardial functional depression. Therapeutic strategies to reduce production or signaling of either TNF-alpha or IL-1beta may limit myocardial dysfunction in **sepsis**.

L13 ANSWER 7 OF 19 MEDLINE

AB Metabolism of macrophage (MO) membrane phospholipids produces key mediators of inflammation and major second messengers that modulate inflammatory responses during **sepsis**. **Sphingomyelin** is a major class of phospholipid that releases ceramide and sphingosine. This study was designed to investigate the involvement of **sphingomyelin** metabolites in MO activation by lipopolysaccharide (LPS). Rabbit alveolar MO were obtained by bronchoalveolar lavage and exposed to C6-ceramide, a cell-permeable analogue of natural ceramide, or sphingosine in the presence of Escherichia coli LPS (100 ng/mL). Tumor necrosis factor (TNF) mRNA expression was measured by Northern blot assays. Total nuclear extract was harvested for the measurement of nuclear factor KB (NFkappaB) with electrophoretic mobility shift assays. MO TNF production was measured by L929 bioassays. C-6 ceramide did not have any effects on MO TNF production or TNF mRNA expression with or without LPS stimulation. Inhibition of ceramide metabolism with 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), or N-oleoyl-ethanolamine (NOE) also did not induce TNF mRNA or TNF production. In comparison, sphingosine inhibited TNF mRNA expression as well as TNF production of LPS-stimulated MO. LPS-induced MO NFkappaB activity was also reduced by sphingosine. Our data indicate that ceramide alone has no effect on macrophage activity, but its metabolite sphingosine down-regulates MO activation induced by LPS

stimulation. Therefore, the **sphingomyelin** pathway is involved in the regulation of MO activation.

L13 ANSWER 8 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
AB Ceramide is a novel second messenger generated by hydrolysis of membrane **sphingomyelin** by a neutral sphingomyelinase (nSMase). Cytokines such as tumor necrosis factor-.alpha. (TNF-.alpha.) have been shown to increase intracellular ceramide through phospholipase A2 (PLA2)-dependent activation of nSMase. TNF-.alpha. has been shown to cause endothelium-independent relaxation in isolated blood vessels. We have previously shown that exogenously applied sphingomyelinase and ceramide cause endothelium-independent vasodilation in rat thoracic aortas (D. G. Johns, H. Osborn, and R. C. Webb. Biochem. Biophys. Res. Commun. 237: 95-97, 1997). In the present study, we tested the hypothesis that ceramide mediates TNF-.alpha.-induced vasodilation. In phenylephrine-contracted rat thoracic aortic rings (no endothelium), TNF-.alpha. caused concentration-dependent relaxation in the presence of cyclooxygenase and lipoxygenase inhibitors. The phospholipase A2 antagonist 7,7-dimethyl-(5Z,8Z)-eicosadienoic acid (DEDA; 50 .mu.M) and the nonselective PLA2 antagonist quinacrine (30 .mu.M) inhibited TNF-.alpha.-induced relaxation. In cultured rat aortic vascular smooth muscle cells, TNF-.alpha. (10-7 g/ml) increased intracellular ceramide 1.5-fold over basal level (0.08 nmol/mg protein), which was blocked by the PLA2 antagonist DEDA (50 .mu.M). We conclude that PLA2 activation and increased ceramide generation play a role in mediating TNF-.alpha.-induced endothelium-independent vasodilation.

L13 ANSWER 9 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB Objective: To compare, using decision analytic techniques, maternal and fetal risk and benefits of three strategies for the management of preterm labour after 32 weeks. These strategies are empiric tocolysis, no tocolysis, or amniocentesis for fetal maturity testing. Data Sources: Published medical literature provided the probabilities, including those for tocolysis efficacy, maternal and neonatal outcomes, and steroid efficacy. Data Synthesis: Separate decision trees were created for hypothetical cohorts of patients presenting with preterm labour at 32, 34, and 36 weeks of gestation to compare strategies. The primary outcome was the total number of expected adverse maternal and neonatal events for each strategy at each gestational age. Results: At 32 weeks tocolysis yielded the lowest total number of adverse maternal and neonatal events. At 34 weeks, both tocolysis and no tocolysis yielded similar overall outcomes. At 36 weeks most clinical outcomes were good regardless of strategy. Conclusions: This analysis supports the empiric use of tocolytics at 32 weeks. At 34 weeks, either tocolysis or no tocolysis appear to be reasonable alternatives. At 36 weeks no tocolysis is probably preferred. This analysis also suggests that amniocentesis should not be employed in the management of preterm labour at these gestational ages.

L13 ANSWER 10 OF 19 MEDLINE DUPLICATE 4
AB The objective of our study is to determine whether aggressive tocolysis in patients with preterm premature rupture of membranes between 24 and 34 weeks gestation improves neonatal outcome. Patients with documented preterm premature rupture of membranes between 24 and 34 weeks gestation were prospectively randomized to group I, aggressive tocolysis with intravenous magnesium sulfate, or to group II, no tocolysis. The lecithin/**sphingomyelin** ratio was determined upon hospital admission and every 48-96 hours until delivery. Both groups received weekly steroids and antibiotics pending culture results and were promptly delivered when chorioamnionitis, fetal stress, or an Lecithin/**sphingomyelin** ratio of > or = 2.0 occurred. The study group involved 145 patients. No statistically significant differences between groups I (n = 78) and II (n = 67) were observed regarding demographic characteristics, gestational age at enrollment or at delivery, latency, development of clinical chorioamnionitis, birth weight, number of days in neonatal intensive care

unit, days on oxygen or ventilatory support, frequency of hyaline membrane disease, necrotizing enterocolitis, intraventricular hemorrhage, neonatal **sepsis**, or neonatal mortality. Our data suggest that tocolysis in patients with preterm premature rupture of membranes does not significantly improve perinatal outcome.

L13 ANSWER 11 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

L13 ANSWER 12 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
AB This study was designed to evaluate neonatal morbidity and mortality following preterm delivery in the setting of mature amniotic fluid pulmonary studies. We performed a retrospective analysis of all pregnancies resulting in preterm deliveries (<37 weeks) from 1/1/88 to 5/31/92 in which there was a 'mature' phospholipid profile, defined as positive phosphatidylglycerol (PG) or lecithin/sphyngomyelin (L/S) ratio .ltoreq. 2 determined within 1 week of delivery. Excluded were multiple gestations, diabetic pregnancies, and fetal or neonatal abnormalities involving the cardiovascular, renal, or pulmonary tract. Main outcome measures were incidence of significant neonatal morbidity, including respiratory distress requiring respiratory support, **sepsis**, patent ductus arteriosus, grade 3-4 intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, meningitis, and pneumonia. A total of 153 patients fulfilled the inclusion criteria. Mean (SD) gestational age at delivery and birth weight were 33.8 (2.1) weeks and 2298 (561) g, respectively. There were no neonatal deaths, but significant morbidity was present in 20% (31/153) of cases. The most common major neonatal complications were respiratory distress (12%) and suspected or documented **sepsis** (16%). Univariate analysis showed that frequency of major neonatal morbidity was related to gestational age at delivery ($p < 0.001$), birth weight ($p < 0.001$), Apgar score at 5 minutes <7 ($p = 0.008$) and method of lung maturity assessment (complications were ore frequent when lung maturity was defined by L/S .ltoreq. 2 than by PG positivity) ($p = 0.02$). Multivariate analysis demonstrated a significant association between the presence of a neonatal complication and method of lung maturity assessment after adjustment for gestational age at delivery ($p = 0.04$). The incidence of major neonatal complications among preterm infants is high even in the presence of mature fetal lung studies; this incidence is related primarily to the gestational age at birth, and secondarily to the method of lung maturity testing (complications are less common in the presence of PG positivity than of L/S .ltoreq. 2).

L13 ANSWER 13 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB Certain phosphatidic/plasmanic/plasmenic acid (PA) species function as lipid intermediates in cell activation and may function directly as intracellular signaling molecules. PA can also be dephosphorylated to 1,2-diradyl-sn-glycerol by phosphatidate phosphohydrolase. Treatment of various cell types, including murine P388 monocytic leukemia cells, with bacterial lipopolysaccharide rapidly stimulates large increases in PA and PA-derived diradylglycerol. Pentoxifylline, 1-(5-oxohexyl)-3,7-dimethylxanthine, inhibits lipopolysaccharide-stimulated formation of PA in P388 cells at high concentrations (IC50 = 500 .mu.M). Lisofylline [1-(5R-hydroxyhexyl)-3,7- dimethylxanthine] is a unique metabolite of pentoxifylline in humans and is >800-fold more active as an inhibitor of PA formation than pentoxifylline (IC50 = 0.6 .mu.M). Lisofylline does not inhibit lipopolysaccharide-induced activation of phosphatidylinositol-specific phospholipase C and generation of phosphatidylinositol-derived diradylglycerol. Lisofylline but not pentoxifylline protects BALB/c mice from endotoxin lethality when administered 4 hr after lipopolysaccharide. This protective effect is independent of either agent's effect on suppression of plasma tumor necrosis factor .alpha.. These data suggest that inhibitors of PA formation may have significant clinical potential in the treatment of **sepsis** and septic shock.

L13 ANSWER 14 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
AB Tumor necrosis factor .alpha. (TNF.alpha.), interleukin 1.beta. (IL-1.beta.), and endotoxin (LPS) are potent pro-inflammatory mediators which induce multiple and diverse biological responses in a wide variety of cell types. However, these pro-inflammatory mediators also have significant overlap and redundancy in their biological effects. This suggests that there is significant diversity in second messenger signal transduction systems induced by these stimuli to explain the diversity in biological responses, as well as significant redundancy. Here we show that one such second messenger common to several proinflammatory stimuli may be phosphatidic acid (PA). Intracellular PA species, which may have intracellular signaling functions, are rapidly induced in P388 monocytic leukemia cells by TNF.alpha., IL-1.beta., or LPS. These PA species vary according to the bond type (i.e., sn-1 ester vs. ether vs. vinyl ether), acyl chain length, and the degree of saturation in the sn-1 and sn-2 positions. Although PA itself may have direct second messenger activities, many of the PA species induced are converted to diacylglycerol species (DG), which are structurally distinct from the DGs generated by phosphatidylcholine-specific phospholipase C (PC-PLC). Lisofylline [(R)-1-(5-hydroxyhexyl)-3,7-dimethylxanthine; LSF] selectively inhibits generation of selected species of PA in P388 cells induced by TNF.alpha., IL-1.beta., or LPS. TNF.alpha.-induced **sphingomyelin** hydrolysis, PLC-mediated PC hydrolysis, and DG kinase-mediated PA formation or TNF.alpha.-induced NF-.kappa.B activation and apoptosis are not inhibited by LSF. LSF has a marked protective effect in a variety of acute inflammatory animal models that may be due to inhibition of this shared second messenger pathway involving PA.

L13 ANSWER 15 OF 19 MEDLINE DUPLICATE 7
AB A retrospective analysis has been performed of perinatal outcome in 81 pregnancies in which preterm premature rupture of membranes (PPROM) was managed using amniocentesis to diagnose intrauterine infection and lung maturity. Ten patients (13%) had a positive Gram stain on microscopy whilst 29 (37%) had a positive culture. Forty-one patients (58%) had a mature lecithin:**sphingomyelin** ratio. There was evidence of **sepsis** in 13 neonates (16%), with a further 16 (20%) being colonized. Both Gram stain and amniotic fluid culture were relatively poor predictors of neonatal **sepsis**. For Gram stain the sensitivity was low at only 15%. Although the sensitivity for culture was higher (69%), the specificity (71%) was too low to be clinically useful. It is recommended that a randomized controlled trial of amniocentesis in PPROM is needed to define the role of this diagnostic test.

L13 ANSWER 16 OF 19 MEDLINE DUPLICATE 8
AB A randomized study was conducted to investigate the effects of antenatal corticosteroids and ampicillin in the management of preterm pregnancies under 34 weeks complicated by premature rupture of membranes. Patients with documented lecithin/**sphingomyelin** (L/S) ratios of less than 2.0 and a singleton gestation were eligible to participate in the study. One hundred sixty-five patients qualified and were randomized, using sealed envelopes, to four study groups. All patients were followed expectantly. Group I (41 patients) received neither ampicillin nor corticosteroids. Group II (43 patients) received 24 mg of antenatal betamethasone. Group III (37 patients) received 2 g of intravenous ampicillin every 6 hours, with discontinuation of antibiotic therapy if cultures were negative for pathogenic bacteria. Group IV (44 patients) received both corticosteroids and ampicillin as described for groups II and III, respectively. Compared with patients not receiving corticosteroids, those administered antenatal corticosteroids experienced a reduction in the incidences of respiratory distress syndrome (53 versus 26%), bronchopulmonary dysplasia (23 versus 9%), severe grades of intracranial hemorrhage (15 versus 3%), and patent ductus arteriosus (18 versus 6%), with no difference in the incidence of maternal or neonatal infection. Compared with patients not receiving antenatal antibiotics, the

group of patients treated with ampicillin on admission had a lower incidence of clinical chorioamnionitis (4 versus 26%) and neonatal **sepsis** (5 versus 10%). This reduction in infectious morbidity by antenatal ampicillin was restricted to those patients (28.4% of the study population) colonized with group B streptococci.(ABSTRACT TRUNCATED AT 250 WORDS)

L13 ANSWER 17 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AB Ambroxol, a drug capable of elevating the phospholipid content in healthy rabbit lungs, was tested on two models of experimental lung injury, lung changes in **sepsis** induced by peritonitis and in bromcarbamide intoxication. The phospholipid content of the lungs and the synthesis of the individual phospholipids phosphatidylcholine (PC) and sphingomyeline were measured in vitro by incubation of lung slices with labeled phospholipid precursors. Influenced by the drug, the phospholipid content increases to 132% in the peritonitis experiments and to 111% in the bromcarbamide experiments. The peritonitis experiments show the increase in phospholipid synthesis to result from an enhanced choline incorporation into PC up to 192% and into sphingomyeline up to 630%. The values for the bromcarbamide experiments are 411% for PC and 485% for sphingomyeline, respectively. There was no statistically significant difference in the incorporation of fatty acids in the treated and untreated animals. We conclude that ambroxol possibly stimulates the phospholipid synthesis in injured lungs by stimulating the choline phosphatidyltransferase, but not the incorporation of fatty acids into PC in those lungs. These findings may be important to the surfactant system of the lung consisting mainly of PC.

L13 ANSWER 18 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB We present the clinical, pathologic, and metabolic findings of an adult woman with debilitating coronary artery disease and hepatosplenomegaly who was discovered to have multiorgan infiltration by sea blue histiocytes. A diagnosis of sea blue histiocyte (SBH) syndrome was made and no further workup performed. The patient suffered from progressive heart failure and **sepsis** following coronary artery bypass surgery and died 9 months after presentation. Tissues examined at autopsy showed pronounced infiltrates of both granular sea blue histiocytes and foamy, vacuolated histiocytes, which were morphologically compatible with Niemann-Pick cells. Ultrastructural examination of these cells revealed lamellar myelin-like figures as described in Niemann-Pick (N-P) disease. Fibroblast enzyme assay studies and liver lipid analyses performed after the patient's death revealed pronounced sphingomyelinase deficiency and a lipid profile diagnostic of N-P disease, type B. This case adds further support to the claim that some cases of apparent SBH syndrome actually represent a type of N-P disease.

L13 ANSWER 19 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB The authors studied changes in erythrocyte in severe infectious syndromes, separating healthy individuals (n=10) from those with hepatic insufficiency No variations variations in sphingomyelins were seen. By contrast, the fall in cholesterol and other phospholipids studied (phosphatidylcholine and phosphatidylethanolamine) was highly significant. The difference between the two groups remained clear on the fourth day. No relationship could be established with prognosis and the organism responsible. In conclusion, the authors stress the need for study of the relationships between these changes and erythrocyte functions.

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